REMARKS

Applicants respectfully request entry of amendments to claims 12-17, and addition of new claim 33. Applicants submit that claims 1-11 and 18-32 were canceled by previous amendment.

Support for the amendments can be found throughout the specification, including p. 13, ll. 5-7, p. 19, ll. 9-11, and the originally filed claims and, therefore, do not add new matter.

Applicants submit that pending claims 12-17 and 33 are in condition for allowance, and respectfully request that the claims as amended be entered.

Rejection Under 35 U.S.C. §112, First Paragraph

Claims 12-17 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement.

Applicants traverse the rejection as applied to the new and amended claims, including claims dependent therefrom, for the reasons given below.

The Office Action alleges, in pertinent part, that the specification is not enabling because at the time of the invention the state of the art as it pertains to the transplantation of neural progenitor cells for therapy were not routinely achievable by those skilled in the art, citing Rossi and Cattaneo (2002); Cao et al. (2002); Milward et al. (1997); Mehler et al. (1999); Kennea et al. (2002); NIH Ad Hoc Committee Report on Gene Therapy (1995); Verma et al.(1997); Friedmann (1997); and Großhans (2000) to support this position.

As a point of clarity, while these references are purported to show the state of the art relative to transplantation of neural progenitor cells for therapy, the claims recite the use of conditionally-immortalized CNS progenitor cells. Applicants submit that the cited references do not provide any evidence that the use of such immortalized progenitor cells was poorly developed or unpredictable, and that in fact Rossi and Cattaneo (2002) demonstrate the opposite is true. For example, while Rossi and Cattaneo (2002) do provide support for the idea that non-immortalized progenitor cells (i.e., neuronal stem cells) are problematic in that they fail to generate multiple local phenotypes, the authors state that "[u]nexpectedly . . . cell lines that have been obtained by immortalizing neural progenitors seem to be endowed with a stronger

propensity to adapt local identities. Indeed, consistent site-specific differentiation has been reported after transplantation of different neural progenitor cell lines into neonatal or adult brain" (Emphasis added) (P. 405, second full paragraph). Rossi and Cattaneo (2002) cite at least five references to support this position, four of which predate the filing of the present application (see below). Respectfully, such a statement in the reference does not support the idea that the immortalized cells as claimed would not be expected to be transplantable, or that Rossi and Cattaneo (2002) provide evidence for lack of enablement of the method as claimed.

Applicants submit that Cao et al. (2002), Milward et al. (1997), Mehler et al. (1999), Kennea et al. (2002), and Großhans (2000) are all limited to non-immortalized cells, and because Rossi and Cattaneo (2002) demonstrate that the properties of immortalized cells are "unexpectedly" different from those of non-immortalized neuronal stem cells, it is clear that one cannot simply extrapolate properties and/or limitations observed for non-immortalized neuronal stem cells to immortalized CNS progenitor cells.

Review of the NIH Ad Hoc Committee Report on Gene Therapy (1995) shows that use of immortalized cells is not mentioned either in the narrative section or the tables describing: (a) systems in use or under consideration for gene therapy (Table 1), (b) delivery vehicles of clinical gene transfer studies (Table 2), or (c) categories of clinical gene transfer protocols (Table 3). The focus of the report was directed to viral vectors, non-viral vectors, liposome complexes, and naked (plasmid) DNA, not cells or ex vivo therapy with immortalized cells. Likewise, the article by Verma et al. (1997) is focused on the use of viral vectors, specifically, retroviral vectors, not cells or ex vivo therapy with immortalized cells. Further, Friedmann (1997) is silent with respect to the immortalized cells as claimed. Again, because the present invention recites the use of conditionally-immortalized CNS progenitor cells, and none of the cited references disparages the use of such cells as envisaged, respectfully, the Office Action has failed to meet its burden in establishing a lack of enablement.

The Office Action goes on to state that the references cited by the Applicants in the previous response were post-filing references, which are alleged not to represent the state of the art at the time of filing. Thus, the Office Action concludes that one of skill in the art would not have had the benefit of the teachings supplied in the cited references with regard to the particular

model systems that are amenable to the transplantation protocols carried out in those studies. While not acquiescing to the reasoning offered in the Office Action, Applicants provide the following pre-filing references which show that indeed, at the time the application was filed, one of skill in the art would have had the benefit of the teachings supplied therein.

Renfranz et al., Cell (1991) 66(4):713-729; Snyder et al., Cell (1992) 68:33-51; Gao and Hatten, Development (1994) 120(5):1059-1070; Shihabuddin et al., J Neurosci (1995) 15(10):6666-6678, which are all cited in Rossi and Cattaneo (2002) (Abstracts/references are provided for Examiner's convenience as Exhibits **A-D**), demonstrate that immortalized cells have the developmental plasticity to respond to local microenvironmental signals and the adult brain retains the capacity to direct differentiation of these cells. For example, Snyder et al. (1992) demonstrates that immortalized cell lines transformed by *v-myc* are capable of engraftment and differentiation into neurons or glia in a manner appropriate to their site of engraftment, where such cells could be identified in animals up to 22 months postengraftment (see Abstract and Results). Gao and Hatten (1994) demonstrate that immortalized cells (in contrast to primary external germ layer (EGL) cells) give rise to multiple types of cells after implantation, and that their finding are consistent with Renfranz et al. (1991), in that immortalized progenitor cells differentiated into a variety of cerebellar cell classes after early implantation (p. 1067, col. 2, second paragraph). Further, Gao and Hatten (1994) were able to show that their results were consistent with Snyder et al. (1992), where it was shown that immortalized cerebellar cells can participate in the formation of the cerebellum (Id.). Moreover, Shihabuddin et al. (1995) were able to demonstrate that immortalized cells showed consistent morphology within their transplantation site, and that, again, immortalized cells have the developmental plasticity to respond to local microenvironmental signals and that the adult brain retains the capacity to direct differentiation of neuronal precursor cells in a direction that is consistent with that of endogenous neurons (e.g., Abstract and Results). With respect to use of such cells to for therapeutic effect, Applicants provide (a) Trotter et al., Glia (1993) 9(1):25-40 (Exhibit **E**), which demonstrates that immortalized cells may be used as transplants for demylinating lesions in spinal cords of adult rats (Abstract) and (b) Tuszynski et al., Gene Therapy (1996) 3:305-314 (Exhibit **F**), which demonstrates (in primates) that intraparenchymal

grafts of genetically modified cells that produce NGF prevent neuronal degeneration (see Abstract and p. 310, col. 1, second paragraph bridging to col. 2, first paragraph).

While it is appropriate to recognize variability in determining the scope of invention, determination of what is needed to support generic claims to biological subject matter depends on a variety of factors including 1) knowledge in the particular field, 2) the extent and content of the prior art, 3) the maturity of the science or technology, and 4) the predictability of the aspect at issue. Capon v. Eshhar, 76 U.S.P.Q.2d 1078, 1084, 418 F.3d 1349, at 1356 (Fed. Cir. 2005).

The present invention represents more than "a mere germ of an idea," the specification supplies the novel aspects of the invention, and it would seem that the use of immortalized cells is certainly not in the nascent stages of development (e.g., p. 1, l. 24 bridging to p. 2, l. 11 of the present application). (See, also, Genentech, Inc. v. Novo Nordisk, 42 U.S.P.Q.2d 101, 108 F.3d 1361 (Fed. Cir. 1997)). Further, in the present specification, not only are the general teachings of how to make the cells of the present invention disclosed (e.g., Example 1), but also specific examples are provided for the production of differentiated cells (e.g., Example 2). Moreover, standardized methods for the treatment of subjects, including routes and frequency of administration, are disclosed (see, e.g., p. 19, l. 18 bridging to p., l. 20, l. 27). And while such procedures involve some level of technical manipulation, because such methods and steps are routinely used in the art, such procedures do not rise to the level of undue experimentation. (See, e.g., Johns Hopkins University v. Cellpro, Inc., 47 U.S.P.Q.2d 1705, 152 F.3d 1342 (Fed. Cir. 1998), where the court stated that "experimentation does not constitute undue experimentation" where "it is merely routine.").

Regarding unpredictability, it is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize the generic invention. See, e.g., In re Angstadt, 537 F.2d 498, 504 (CCPA 1976). Accordingly, generic inventions are not *per se* invalid because success for each possible iteration is not assured. Capon, at 1357.

Therefore, the claims are enabled because the specification provides appropriate guidance, working examples, and prediction of function based on the observed properties of

immortalized CNS progenitor cells such that one of skill in the art could practice the invention as claimed, in the absence of undue experimentation.

For these reasons, Applicants respectfully request that the rejection, including as it may be applied to the amended claims, be withdrawn.

Conclusion

Applicants submit that pending claims 12-17 and 33 are in condition for allowance. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this submission.

Please charge Deposit Account 07-1896 in the amount of $870.00 for a Request for Continued Examination fee and a Three Month Extension of Time (minus a previously paid One Month Extenion) fee. The Commissioner is hereby authorized to charge any additional fees required by this submission, or make any credits or overpayments, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

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